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(54) Title: ENZYME-SENSITIVE ENTERIC PREPARATION FOR ORAL ADMINISTRATION

(57) Abstract

The object of the invention is to provide an enteric preparation which has higher specificity and is enzyme-sensitive. The preparation wherein a medicine is dissolved in a vehicle containing one or more fatty acids selected from a group consisting of glycerol fatty acid ester, polyoxyethylene sorbitan fatty acid ester, propylene glycol fatty acid ester, polyethylene glycol fatty acid ester, ethylene glycol fatty acid ester and decaglycerol fatty acid ester.

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ENZYME-SENSITIVE ENTERIC PREPARATION FOR ORAL ADMINISTRATION

FIELD OF THE INVENTION

The present invention provides a new means for administering pharmaceutical compounds orally.

The present invention relates to an enzyme-sensitive enteric pharmaceutical preparation for oral administration. More particularly, it relates to an enzyme-sensitive enteric pharmaceutical preparation which, after administered, releases a medicine in the small intestine by degradation of an oily vehicle (liquid carrier in a capsule, or pellet) by a pancreatic lipase or esterase.

INFORMATION DISCLOSURE

U.S. Patent No. 3,688,763 and Japanese KOKAI 49060289 describe enteric coated capsules subject to enzyme degradation.

With regard to a medicine which induces gastric disorder during stay in the stomach, or is unstable in the

stomach, there is means to enhance activities of the medicine by formulating it into an enteric pharmaceutical preparation. Such enteric pharmaceutical preparations which are presently marketed are those depending upon (or is sensitive to) pH. That is, since pH in the stomach is generally in acidic range and pH in the small intestine is neutral range, the preparations are therefore obtained by coating on tablets or granules with polymers which degrade in neutral pH range but not in acidic pH range (e.g., celullose derivative or Eudragit) [see I.Mharaj et al., J.Pharam.Sci., volume 73, page 59, 1988; S. Y.Lin et al., Pharm.Res., volume 4, page 70, 1987].

However, in practice, the time and the body site required for reaching the pH at which a medicine is released vary depending upon by not only individuals but also by situations of the same individual, which results in change of bioavailability or effect. For example, it is known that, since pH of gastric solution of some patients rises (to near neutral pH), a medicine contained in the above-described pH sensitive enteric preparation is released in the stomach and the purpose as an enteric pharmaceutical preparation can not be obtained [see H.MAEKAWA et al., Yakuzaigaku, volume 4, page 135-141, 1970].

Technical Problem:

Under these circumstances, a more specific enteric pharmaceutical preparation is desired. As one means, it is considered that the use of a material which is degraded by an enzyme having a higher activity in the small intestine as a vehicle can impart higher enteric specificity regardless of the pH in the stomach.

In this regard, aiming at the fact that triglycerides are rapidly degraded in the small intestine by a pancreatic lipase in the presence of bile acid, there has been reported a possibility of formulating a water-soluble medicine into a preparation by simply suspending it in triglycerides [see Toshiaki NISHIHATA et al., J. Pharm. Pharmacol., volume 38, pages 69-70, 1986]. And, as examples of utilization of the above-described technique (for suspending a medicine in triglycerides), there have been proposed small particles of triglycerides [see Hironori YOSHITOMI et al., Yakuzaigaku, volume 50, pages 156-165, 1990] and triglyceride granules [see Mitsuso MATSUMOTO et al., Int.J.Pharm., volume 64, pages 147-154, 1990].

Although these are enteric preparations wherein small particles or granules disintegrate by a pancreatic lipase and thereby a medicine is released, this kind of dosage forms are fundamentally similar to those of triglyceride suppositories. Therefore, they have similar

defects to those of the triglyceride suppositories. That is, firstly, since a medicine is in a suspended state, uniformity of a medicine in the preparation requires special processes. Secondly, sometimes, storage in cold places is required for preservation. Further, since granules of a medicine (having the particle size of not less than a few microns) are in a suspended state, a water-very slightly soluble medicine can not be smoothly released after disintegration of the preparation in the small intestine.

Thus, the object of the present invention is to solve the problem of the above-described proposal and provide a pharmaceutical preparation which is enzyme-sensitive rather than pH-sensitive and is improved in enteric specificity.

The second object of the present invention is to provide a preparation wherein a medicine is dispersed uniformly therein, particularly in a fashion of monomolecular dispersion, because such the dispersion leads to improvement in absorbability and productivity of a very slightly soluble medicine. In this regard, a preparation wherein triglyceride having extremely low potency as a solubilizer can not accomplish this object.

Further, the object of the present invention is to provide an enzyme-sensitive pharmaceutical preparation having excellent storage stability.

Solution for Technical Problem:

The present inventors have tried various methods. As a result, it has been unexpectedly found that the above object can be accomplished by firstly selecting oils of fatty acid esters which are easily degraded by an esterase in addition to pancreatic lipase having higher activity in the small intestine, and then selecting oils (solubilizers) which have higher potency for solubilizing a medicine, and further selecting oils which have higher partition coefficient from the selected oils.

That is, the present invention provides an enzyme-sensitive enteric pharmaceutical preparation for oral administration characterized in that a medicine is dissolved in a vehicle containing one or more fatty acid esters selected form a group consisting of glycerol fatty acid ester (monoester, diester), polyoxyethylene sorbitan fatty acid ester, propylene glycol fatty acid ester, polyethylene glycol fatty acid ester, ethylene glycol fatty acid ester and decaglycerol fatty acid ester.

Firstly, the medicines to be contained in the pharmaceutical preparation of the present invention are not specifically limited. However, in comparison with the conventional techniques, a medicine having influence on

stomach disorder, a medicine which is unstable in gastric solution (including ones having unstable fundamental structure, or a medicine of which properties changes by desalting from a salt of the compound) can be contained. As examples of the medicine having influence on stomach disorder, there are nonsteroidal antiphlogistic and analgesic agents (indomethacin, sodium diclofenac, aspirin) and general aromatic halogenated compound, and as examples of other medicines, there are antianxiety agents (U-78875 (merchandise number of THE UPJOHN COMPANY), thrombolytic agents (itazigrel), anti-malignant tumor agents (menogaril, bropyrimine) and vitamins (vitamin A palmitate, vitamin K_3, tocopherol, ubiquinone, coenzyme-type vitamin B_{12}, biotin) and the like. One or more these medicines can be contained in the preparation of the present invention.

In the present invention, the above medicine are contained in the preparation by dissolving them in a particular solubilizer. As this solubilizer, those having higher sensitivity to pancreatic lipase or esterase which is an enzyme having higher activity in small intestine are used. This time, it has been found that, by using such the enzyme-sensitive solubilizer, the specific properties for releasing a medicine in small intestine is improved.

As such the enzyme-sensitive solubilizer, there are fatty acid esters which are known as a nonionic

surfactant, that is, glycerol mono-fatty acid ester (glycerol mono-caprate, glycerol mono-myristate, glycerol mono-stearate, glycerol mono-oleate etc.), glycerol di-fatty acid ester (glycerol di-caprylate, glycerol di-myristate, glycerol di-stearate, glycerol di-oleate etc.), polyoxyethylene sorbitan fatty acid ester (polyoxyethylene sorbitan mono-oleate (polysorbate 80), polyoxyethylene sorbitan mono-stearate, polyoxyethylene sorbitan mono-palmitate etc.), propylene glycol fatty acid ester (propylene glycol mono-caprylate, propylene glycol mono-iso-octanate, propylene glycol di-caprylate, propylene glycol di-caprate etc.), ethylene glycol fatty acid ester (ethylene glycol mono-caprate, ethylene glycol di-caprylate etc.), polyethylene glycol fatty acid ester (polyethylene glycol mono-stearate, polyethylene glycol mono-oleate, polyethylene glycol mono-laurate), decaglycerol fatty acid ester (decaglycerol mono-oleate) and the like. Among these, polysorbate 80, glycerol mono-caprylate, glycerol mono-stearate, polyethylene glycol mono-stearate are preferable. In addition, these solubilizers may be also appropriately used as a mixture of more than one of them.

The amount of the solubilizer to be used can be appropriately selected depending upon the kind of a particular solubilizer, a particular medicine to be dissolved, purpose of the use and the like. In any event,

the solubilizer is used in an amount to dissolve the medicine.

Next, production of the enzyme-sensitive enteric pharmaceutical preparations for oral administration of the present invention will be explained below. Among solutions wherein a medicine is dissolved in an enzyme-sensitive solubilizer, one which is liquid at room temperature can be used as it is as the pharmaceutical preparation of the present invention, or it can be filled into a soft capsule or a hard capsule. And, one which is solid at room temperature can be formulated in a pellet or filled in a hard capsule by warming the solubilizer to melt, dissolving a medicine therein and cooling it to room temperature. In addition, a solubilizer having higher melting point can be added to a preparation which contains a medicine having relatively low partition coefficient in order to improve its properties that it holds the medicine until the desired degradation, which results in improvement of specific enteric properties.

The production can be conducted according to the conventional method. For example, a predetermined amount of the medicine and a sufficient amount of the above-described enzyme-sensitive solubilizer to dissolve the medicine are mixed well using an aquamizer (manufactured by Hosokawa Micron Ltd.) to dissolve the medicine completely, then the

mixture is filled into a soft capsule or a hard capsule with an encapsulating machine. On the other hand, pellets are produced using a pelletizer. The amount of the medicine in the pharmaceutical preparation can be appropriately selected depending upon a particular medicine, the use purpose and the like. In addition, other ingredients which are conventionally used in production of the pharmaceutical preparations may be optionally added.

An enzyme-sensitive enteric pharmaceutical preparation of the present invention thus obtained can be orally administered. An oily vehicle of the pharmaceutical preparation which has been administered holds the medicine therein in gastric solution even if it should be dispersed, which results in no release of the medicine. As this administered oily vehicle reaches duodenum, it is degraded by pancreatic lipase or esterase, and the medicine contained in it is released by disintegration of the dosage form. Since the medicine is in the monomolecularly dispersed (dissolved) state, the medicine which is released after dedradation of the oily vehicle is rapidly absorbed from small intestine even if the medicine is very slightly soluble. As a result, reprecipitation dose not occur and the absorbability becomes excellent. In addition, a pellet dosage form holds its own form in gastric solution after administration, and when it reaches duodenum, it is dedraded

by pancreatic lipase or esterase and the medicine is released by disintegration of the dosage form.

Process for selecting the vehicle solubilizer to be used in the present invention and good enteric properties are explained below by experimental data.

Experiment 1 Examination of an enzyme-sensitive oily solubilizer vehicle

Degradation by lipase or esterase of a fatty acid ester which is an enzyme-sensitive oily solubilizer was examined as follows. To 100 ml of 0.05 M phosphate buffer (pH 6.8) containing bovine pancreatic lipase (4μg/ml) or esterase (10 μg/ml) and sodium taurocholate (24 mM) added 500 mg of a test solubilizer, and temperature was kept at 37 °C in water bath while shaking. A sample solution for measuring the degradation was collected at 15, 30 and 60 min., and free fatty acid in the collected sample which had been produced by degradation was quantitated using a commercially available free fatty acid measuring kit (NEFA-Test, manufacture by Wako Junyaku).

Fig 1 shows degradation by pancreatic lipase or esterase of glycerol mono-caprylate, propylene glycol di-caprylate, polysorbate 80, polyethylene glycol mono-stearate, glycerol mono-stearate and a mixed oily solubilizer. It can be understood from Fig 1 that, although

degrading velocity differs depending upon a kind of oily solubilizer and sensitivity relative to lipase or esterase, the velocity of the tested solubilizers is high.

Experiment 2 Solubility of a medicine in an enzyme-sensitive oily solubilizer

Solubility of a medicine in an enzyme-sensitive oily solubilizer was measured at room temperature, 40 °C, 50 °C and 60 °C. This was done based on the melting point of a solubilizer because one which is solid at room temperature is used to dissolve a medicine at the temperature above its melting point. The measuring was carried out according to the conventional method [see Toshiaki NISHIHATA et al., Chem.Pharm.Bull, volume 39, pages 509-511, 1991]. Table 1 shows solubility of a medicine such as itazigrel, indomethacin, U-78875 etc. in various oily solubilizers.

Table 1

Solubility of a medicine in fatty acid ester oil (mg/g)

	Testosterone	Itazigrel	Indomethacin	U-78875	Vitamin A palmitate	Dl-q tocopherol
25 °C						
Glycerol mono-caprylate	15	70	20	30	500	500
Propylene glycol di-caprylate	100	150	5	2	500	500
Polysorbate 80	20	180	70	13	200	200
Ethylene glycol mono-caprylate	100	-	15	-	550	500
Ethylene glycol di-caprylate	15	-	5	-	500	500
40 °C						
Glycerol mono-caprylate	85	25	35			
Polysorbate 80	250	85	15			
50 °C						
Polyethylene glycol mono-stearate	>50	>10	>5			
60 °C						
Glycerol mono-stearate	>200	>100	>25			

From Table 2, it can be understood that, in particular, glycerol mono-caprylate and polysorbate 80 are excellent solubilizers and the solubility properties of propylene glycol di-caprylate significantly differs depending upon a particular medicine to be used.

Polyethylene glycol mono-stearate and glycerol mono-stearate are semisolid at room temperature. But they can dissolve a medicine therein after they have been melted, and disperse a medicine in the monomolecular state, so they can be adopted as an oily solubilizer in the present preparation. In addition, in particular, these two oily solubilizers having the higher melting point can be used as an additive for keeping the melting point of a solubilizing vehicle for a medicine having relatively not good partition coefficient at the temperature slightly above bodily temperature as shown in the below Experiment.

Experiment 3 Partition coefficient of a medicine

Since an enzyme-sensitive enteric preparation is on the assumption that it should not release a medicine in stomach, it is necessary that a medicine should be held in an oily solubilizer. For this purpose, it is fundamentally required that a solubilizer which endow a medicine to be contained therein with higher partition coefficient should be selected. Table 2 shows a part of experimental

results. Test of partition between oil phase and water phase was carried out according to the conventional method [see Toshiaki NISHIHATA et al., Pharmaceutical Research, volume 7, pages 1302-1306, 1990]. Additionally, since test of partition between water and oil was aimed to simulate the state of the preparation in gastrointestinal tract, volumes of water phase and oil phase were selected as follows. That is, water phase was used in an amount of 100 g while oil phase was used in an amount of 0.25g, and the test was carried out at 37 °C while shaking.

Table 2

Oil-water partition coefficient

(oil phase/water phase) (37 °C)

Oil phase	Water phase	Itazigrel	Indomethacin	U-78875
Glycerol	1.2	$>5x10^5$	$>5x10^5$	ca. 200
mono-caprylate	6.8	$>5x10^5$	ca.4000	ca. 250
Propylene glycol	1.2	$>10^7$	$>10^7$	ca. 150
di-caprylate	6.8	$>10^7$	ca. 100	ca. 150
Polysorbate 80	1.2	$>5x10^6$	$>2x10^4$	ca. 100
	6.8	$5x10^5$	ca.2000	ca. 100

As shown in Table 2, itazigrel exhibits higher partition coefficient in glycerol mono-caprylate, propylene glycol di-caprylate and polysorbate 80 irrespective of pH change in water phase and its partition coefficient in oil

phase is not less than 100 thousands. This result shows that, when 1 g of an oily vehicle is contained in 100 ml of digestive liquid, 99.9% of a medicine is in the vehicle and 0.1% of the medicine is in digestive liquid. Indomethacin exhibits higher partition coefficient in glycerol mono-caprylate or polysorbate 80. However, there are oily vehicles such as U-78875 having about 100 of partition coefficient. With respect to an oil vehicle having relatively not higher partition coefficient, release of a medicine in stomach can be inhibited by solidification of the preparation as described below.

Examples:

Following Examples illustrate the present invention in detail.

Example 1

According to the conventional method, 2 g of itazigrel was dissolved in 100 g of glycerol mono-caprylate, and each 250 mg of the solution was filled into a hard capsule or soft capsule as a support to obtain 400 preparations of the present invention, respectively.

Example 2

According to the conventional method, 2 g of indomethacin was dissolved in 100 g of glycerol mono-caprylate, and each 250 mg of the solution was filled into a

hard capsule or soft capsule as a support to obtain 400 preparations of the present invention, respectively.

Example 3

According to the conventional method, 2 g of U-78875 was dissolved in 100 g of glycerol mono-caprylate, and each 250 mg of the solution was filled into a hard capsule or soft capsule as a support to obtain 400 preparations of the present invention, respectively.

Example 4

According to the conventional method, 15 g of itazigrel was dissolved in 100 g of polysorbate 80, and each 250 mg of the solution was filled into a hard capsule or soft capsule as a support to obtain 400 preparations of the present invention, respectively.

Example 5

According to the conventional method, 5 g of indomethacin was dissolved in 100 g of polysorbate 80, and each 250 mg of the solution was filled into a hard capsule or soft capsule to obtain 400 preparations of the present invention, respectively.

Example 6

According to the conventional method, 1 g of U-

78875 was dissolved in 100 g of polysorbate 80, and each 250 mg of the solution was filled into a hard capsule or soft capsule as a support to obtain 400 preparations of the present invention, respectively.

Example 7

According to the conventional method, 5 g of itazigrel was dissolved in a mixture solution of 50 g of glycerol mono-caprylate and 50 g of glycerol mono-stearate which had been warmed to 60 °C, then 50 mg pellets were made by a pelletizer at room temperature.

Example 8

According to the conventional method, 5 g of indomethacin was dissolved in a mixture solution of 50 g of glycerol mono-caprylate and 50 g of glycerol mono-stearate which had been warmed to 60 °C, then 50 mg pellets were made by a pelletizer at room temperature.

Example 9

According to the conventional method, 5 g of U-78875 was dissolved in a mixture solution of 50 g of glycerol mono-caprylate and 50 g of glycerol mono-stearate which had been warmed to 60 °C, then 50 mg pellets were made by a pelletizer at room temperature.

Example 10

According to the conventional method, 5 g of itazigrel was dissolved in a mixture solution of 50 g of glycerol mono-caprylate and 50 g of mono-stearate which had been warmed to 60 °C, then 50 mg pellets were made by a pelletizer at room temperature.

Example 11

According to the conventional method, 5 g of indomethacin was dissolved in a mixture solution of 50 g of glycerol mono-caprylate and 50 g of glycerol mono-stearate which had been warmed to 60 °C, then 50 mg pellets were made by a pelletizer at room temperature.

Example 12

According to the conventional method, 5 g of U-78875 was dissolved in a mixture solution of 50 g of glycerol mono-caprylate and 50 g of glycerol mono-stearate which had been warmed to 60 °C, then 50 mg pellets were made by a pelletizer at room temperature.

Experiment 4 Release of a medicine from an enzyme-sensitive oily vehicle

With respect to medicines having higher partition coefficient in oil phase, release test was carried out using liquid oily vehicles. Release test from a liquid oily

vehicle was carried out by putting each one capsule from Examples 1 to 6 into a conical tube filled with 50 ml of test solution. As the test solution, Solution 1 and Solution 2 of Disintegration Test in Japanese Pharmacopoeia as well as the same containing pancreatic lipase or esterase were used. Fig 2 or Fig 3 shows the results when itazigrel or indomethacin was used as a medicine, respectively.

As shown in Fig 2, with respect to itazigrel, no release from glycerol mono-caprylate or polysorbate 80 was observed in Solution 1 and Solution 2. In the test solution wherein lipase was contained in Solution 2, remarkably rapid release of itazigrel from glycerol mono-caprylate vehicle was observed. From this, the pharmaceutical preparation of Example 1 using glycerol mono-caprylate is clearly a lipase-sensitive enteric preparation. Further, release of itazigrel from polysorbate 80 vehicle was remarkably observed when esterase was contained in Solution 2. From this, the pharmaceutical preparation using polysorbate 80 is clearly an esterase-sensitive enteric preparation.

Fig 3 shows release behavior of indomethacin from indomethacin pharmaceutical preparation using glycerol mono-caprylate or polysorbate 80 as an oily vehicle. Release of indomethacin was not observed at all in Solution 1, but a few % of release from glycerol mono-caprylate within 1 hour

and about 10 % of release from polysorbate 80 were observed in Solution 2. When lipase was contained in these two Solutions, about 90 % of release of indomethacin from glycerol mono-caprylate vehicle was observed at 15 min., and from this, it can be understood that the pharmaceutical preparation of Example 2 is a good lipase-sensitive enteric preparation. Further, polysorbate 80 vehicle showed remarkably increased release in Solution 2 containing esterase. From this, it can be understood that the pharmaceutical preparation of Example 5 is a good esterase-sensitive enteric preparation.

Experiment 5

Next, release properties of pharmaceutical preparations of the present invention obtained in Examples 7 to 12 were examined. Test solutions were prepared according to the procedures in the above-described Experiment 4. As shown in Fig 4, release of itazigrel was observed in neutral pH test solutions only when lipase or esterase was contained. This result shows that the pharmaceutical preparations of Examples 7 and 10 are a lipase or esterase-sensitive enteric preparation. As shown in Fig 5, in Solution 1 and Solution 2 in Japanese Pharmacopoeia, release of indomethacin from pellets of Examples 8 and 11 is not more than 2 % at 2 hour while release of indomethacin from a pellet from Example 8 is about 60 % at 30 min. in the

presence of lipase. And release from a pellet of Example 11 was also remarkably observed in the presence of esterase. With respect to a pellet of Example 9 or 12 which contains U-78875, release of a medicine was not more than 5 % at 60 min. in Solutions 1 and 2 as shown in Fig 6. On the contrary, a pellet of Example 9 showed about 80 % of medicine release at 60 min. in Solution 2 containing lipase. Further, a pellet of Example 12 showed 50 % of release at 60 min. in Solution 2 containing esterase. This experimental result shows that both pellets of Examples 9 and 12 are an enzyme-sensitive enteric preparation.

Experiment 6

Next, preparations containing a pigment were prepared, and release properties in small intestine was tested in vivo.

Preparation of test sample 1

According to the conventional method, 25 g of Sudan II (red pigment) was dissolved in 1 kg of glycerol mono-caprylate to obtain a test sample preparation.

Preparation of test sample 2

According to the conventional method, 25 g of Sudan II was dissolved in 1 kg of polysorbate 80 to obtain a test sample preparation.

Preparation of test sample 3

According to the conventional method, 25 g of Sudan II was dissolved in 1 kg of a 4:3 mixture of glycerol mono-caprylate and glycerol mono-stearate at 50 °C, and solidified at room temperature to obtain 50 mg pellets for test sample.

Preparation of test sample 4

According to the conventional method, 25 g of Sudan II was dissolved in 1 kg of a 1:2 mixture of polysorbate 80 and polyethylene glycol mono-stearate, and solidified at room temperature to obtain 50 mg pellets for test sample.

Preparations of the above test samples 1 to 4 were orally administered to a rat (preparation weight: 500 mg), celiotomy was carried out after 1.5 hours, a gastrointestinal tract was isolated, and the stained state of gastric membrana mucosa and small intestinal membrana mucosa was observed. After celiotomy of the gastrointestinal tract, the surface of the membrana mucosa was washed by physiological saline, and the stained state was observed with the naked sight. As a control, 500 mg of 0.5% CMCNa suspension containing 2.5% of Sudan II was administered. Results are shown in Table 3. Further, as a nonreleasing control, ten of 500 mg pellets made of bees wax

containing 2.5% w/w Sudan II were administered. In addition, all were collected after washing, ethanol was added to 250 ml, and centrifuged, then the concentration of Sudan II in supernatant was measured to calculate the amount of recovered Sudan II.

Table 3

Stained state of membrana mucosa of gastrointestinal tract at 1.5 hours after administration of the preparation containing Sudan II and recovery rate of Sudan II from contents in gastrointestinal tract

Preparation	Stained state		Recovery rate
	Gastric mucosa	Duodenal mucosa	
Suspension*	+++	+++	78±15%
Bees wax pellet**	-	-	98±13%
Test sample 1	-	+++	38±10%
Test sample 2	-(±)	+++	46± 8%
Test sample 3	-	+++	54±12%
Test sample 4	-	+++	62± 9%

+++: remarkably stained, ++: remarkably stained, but distinct in shade of color

+: restricted in stained part, ±: difficult to determine the stained state with the naked sight

-: no observation of the stained state with the naked

sight

*: administration of Sudan II which was suspended in 0.5% carboxymethylcellulose sodium solution

**: pellet obtained by melting bees wax at 70 °C, suspending Sudan II therein, and solidifying it at room temperature

As shown in Table 3, remarkably stained state was observed in gastric membrana mucosa and the stained state in small intestinal membrana mucosa was observed after 2.5 % Sudan II suspension as a control had been administered, and it was, therefore, recognized that this pigment stains the membrana mucosa of gastrointestinal tract including membrana mucosa by being released from the preparation. Rate of Sudan II which was absorbed from contents in cavity of gastrointestinal tract at 1.5 hours was about 75 %. And, after administration of bees wax pellet which was used as a negative control, Sudan II remained held in the preparation, and the stained state of gastrointestinal tract membrana mucosa was not observed and the presence of a pellet itself was confirmed. At 1.5 hours after administration, the recovery rate of Sudan II from contents in cavity of gastrointestinal tract was about 100%. When a liquid vehicle preparation of test sample 1 was orally administered, the stained state of gastric membrana mucosa was not recognized at all, but the remarkably stained state

of small intestinal membrana mucosa (in particular, duodenal membrana mucosa) was recognized. This result shows that the preparation of test sample 1 dose not release Sudan II in stomach and remarkably releases Sudan II in duodenum, therefore the preparation is an enteric preparation. And, the recovery rate of Sudan II from the gastrointestinal tract is about 35% at 1.5 hours, it is shown that absorption of Sudan II from small intestine is remarkable after administration of this preparation in comparison with the case of suspension. Therefore, it was confirmed that this preparation is an enzyme-sensitive enteric preparation in the animal test. When a liquid vehicle preparation of test sample 2 was orally administered, the stained state of gastric membrana mucosa was not recognized at all or slightly even if recognized. On the contrary, in small intestinal membrana mucosa, the remarkably stained state was recognized. This result shows that the preparation of test sample 2 dose not release Sudan II in stomach or slightly even if it releases the pigment while it releases much in small intestine, and further that the recovery rate of Sudan II from the gastrointestinal tract at 1.5 hours after administration is about 45 % and absorption of Sudan II from small intestine after administration of the preparation is remarkable in comparison with the case of suspension. Therefore, it was confirmed in the animal test that this preparation is an enzyme-sensitive enteric preparation, and

it was found at the same time that the preparation has also the properties to improve absorbability of very slightly soluble material.

In addition, the stained state of gastric membrana mucosa was not observed at all, when the pellet preparation of test sample 3 or 4 was administered, respectively. On the contrary, the remarkably stained state was observed in small intestinal membrana mucosa, and it was confirmed also in the animal test that both preparations are an enzyme-sensitive enteric preparation. And, the recovery rate of Sudan II from contents in cavity of gastrointestinal tract at 1.5 hours was about 55% after administration of the pellet of test sample 3 and about 60% after administration of test sample 4. Since remarkable improvement was recognized in comparison with the case of suspension, it was confirmed that these preparations also improve the absorbability of very slightly soluble material.

Effect of the invention:

According to the present invention, there is provided an enzyme-sensitive enteric preparation which is not pH-sensitive and has improved specificity for releasing a medicine by being degraded in small intestine.

Since such the preparation of the present invention is of type that a medicine is dissolved, it has

uniform dispersion of a medicine and good absorbability of a very slightly soluble medicine. And, since the present preparation requires no special processes to obtain uniformity, it is excellent in productivity of the preparation.

Further, the present preparation dose not require storage in the cold places, and it can be stored at room temperature.

Brief Description of the Drawings:

Fig 1 is a graph showing degradation behavior when sample oily solubilizers were degraded by lipase or esterase. Fig 1 (A) is the case where the fatty acid ester is glycerol mono-caprylate or propylene glycol di-caprylate, Fig 1 (B) is the case where the fatty acid ester is polysorbate 80 or polyethylene glycol mono-stearate, and Fig 1 (C) is the case where the fatty acid ester is glycerol mono-stearate, a mixture of glycerol mono-stearate and polysorbate 80, or a mixture of glycerol mono-caprylate and glycerol mono-stearate.

Fig 2 is a graph showing the releasing behavior of itazigrel from the preparation obtained in Examples, and Fig 2 (A) is the case of the preparation of Example 1 and Fig 2 (B) is the case of the preparation of Example 4.

Fig 3 is a graph showing the releasing behavior of indomethacin from the preparations obtained in Examples, and Fig 3 (A) is the case of the preparation of Example 2 and

Fig 3 (B) is the case of the preparation of Example 5.

Fig 4 is a graph showing the releasing behavior of itazigrel from the preparations obtained Examples, and Fig 4 (A) is the case of the preparation of Example 7 and Fig 4 (B) is the case of the preparation of Example 10.

Fig 5 is a graph showing the releasing behavior of indomethacin from the preparations obtained in Examples, and Fig 5 (A) is the case of the preparation of Example 8 and Fig 5 (B) is the case of the preparation of Example 11.

Fig 6 is a graph showing the releasing behavior of U-78875 from the preparations obtained in Examples, and Fig 6 (A) is the case of the preparation of Example 9 and Fig 6 (B) is the case of the preparation of Example 12.

FIGURE LEGENDS

Fig. 1(A) ○ and , glycerol monocaprylate; △ and ▲, propylene glycol di-caprylate

Fig. 1(B) ○ and ●, polysorbate 80; △ and ▲, polyethylene glycol mono-stearate

Fig. 1(C) ○ and ●, glycerol mono-stearate; △ and ▲, 1:1 (rate of weight) mixture of glycerol mono-stearate and polysorbate 80; □ and ■, 1:1 (rate of weight) mixture of glycerol mono-caprylate and glycerol mono-stearate

Symbols○, △ and □ designate the results when lipase is present, and ●, ▲ and ■ designate the results when esterase is present.

Fig. 2(A) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing lipase used in Experiment 1

Fig. 2(B) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing esterase used in Experiment 1

Fig. 3(A) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing lipase used in Experiment 1

Fig. 3(B) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing esterase used in Experiment 1

Fig. 4(A) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing lipase used in Experiment 1

Fig. 4(B) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
, Test solution containing esterase used in Experiment 1

FIGURE LEGENDS (CONTINUED)

Fig. 5(A) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing lipase used in Experiment 1

Fig. 5(B) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing esterase used in Experiment 1

Fig. 6(A) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing lipase used in Experiment 1

Fig. 6(B) ○, Solution 1 or 2 in Japanese Pharmacopoeia as test solution
●, Test solution containing esterase used in Experiment 1

CLAIMS

1. An enzyme-sensitive enteric pharmaceutical preparation for oral administration characterized in that a medicine is dissolved in a vehicle containing one or more fatty acid esters selected from a group consisting of glycerol fatty acid ester, polyoxyethylene sorbitan fatty acid ester, propylene glycol fatty acid ester, polyethylene glycol fatty acid ester, ethylene glycol fatty acid ester and decaglycerol fatty acid ester.

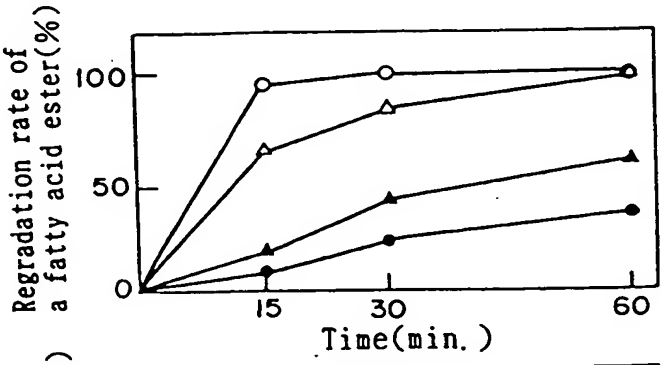
2. A preparation of Claim 1 wherein the medicine is 3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-(1-methylethyl)-imidazo[1,5-a]-quinoxalin-4(5H)-one (U-78875), itazigrel, or indomethacin.

3. A preparation of Claim 2, wherein the medicine is 3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-(1-methylethyl)-imidazo[1,5-a]-quinoxalin-4(5H)-one.

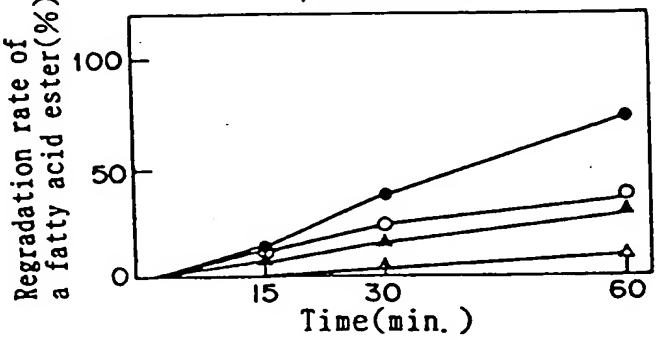
Fig. 1/6

Regradation by lipase or esterase of a sample of an oily solubilizer

(A)



(B)



(C)

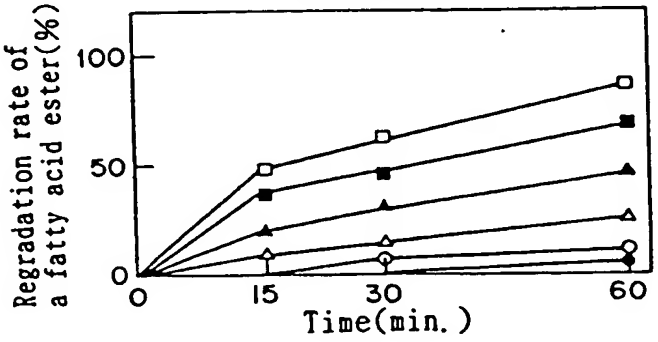
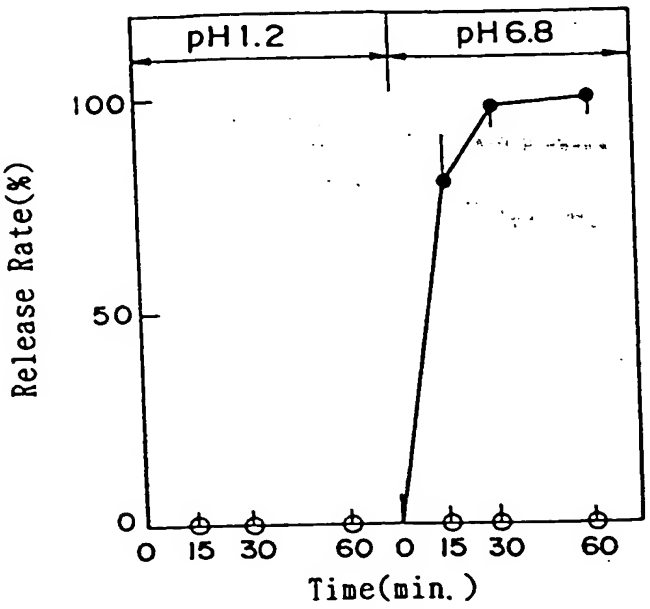


Fig. 2/6

Release behavior of itazigrel from the preparation of Example 1(A) or Example 4(B)

(A)



(B)

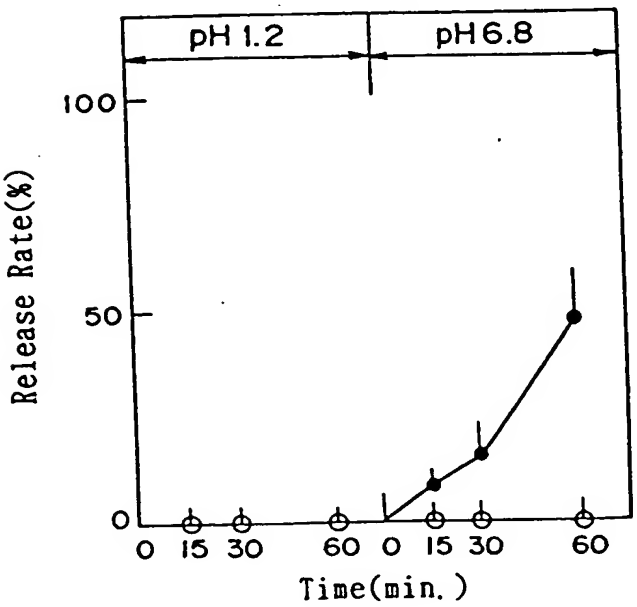
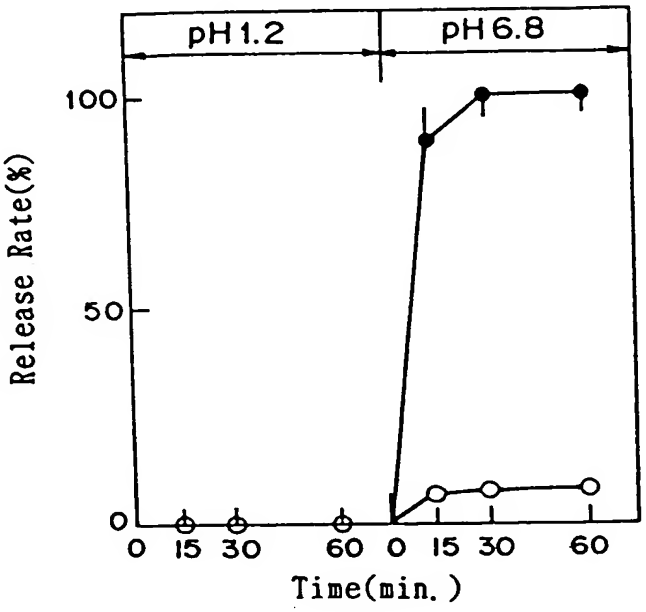


Fig. 3/6

Release behavior of indomethacin from the preparation of Example 2(A) or Example 5(B)

(A)



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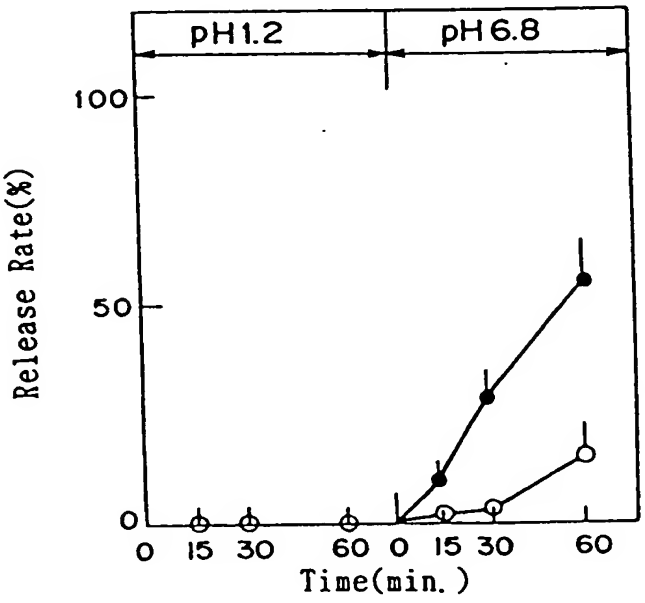
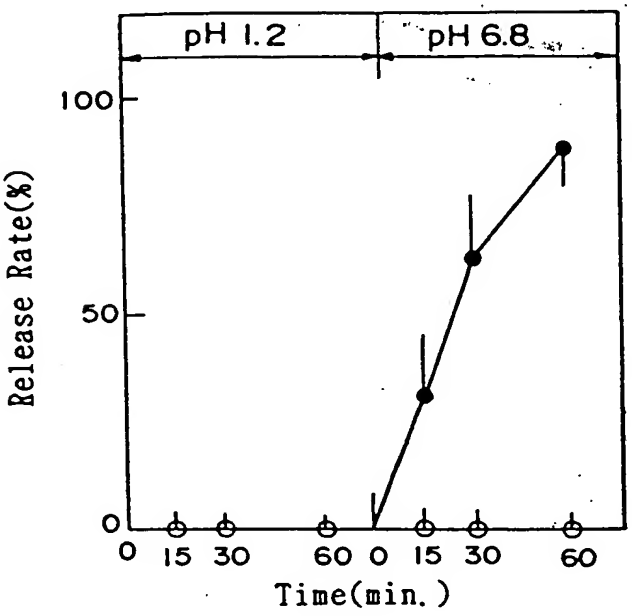


Fig. 4/6

Release behavior of itazigrel from pellets preparation of Example 7(A) or Example 10(B)

(A)



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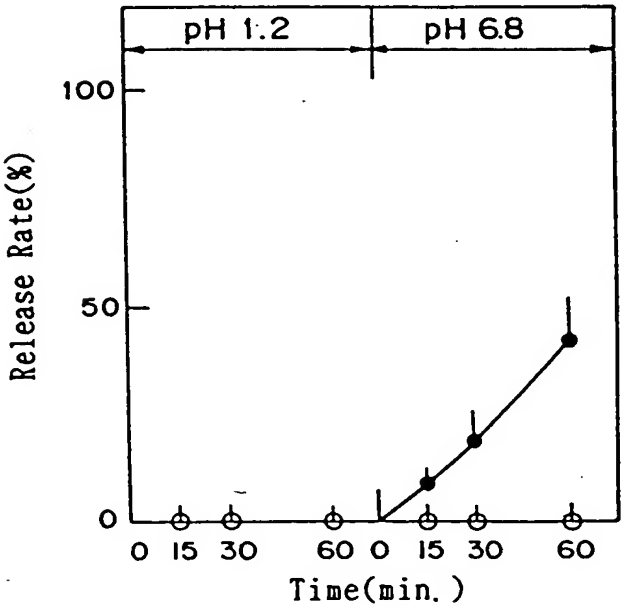
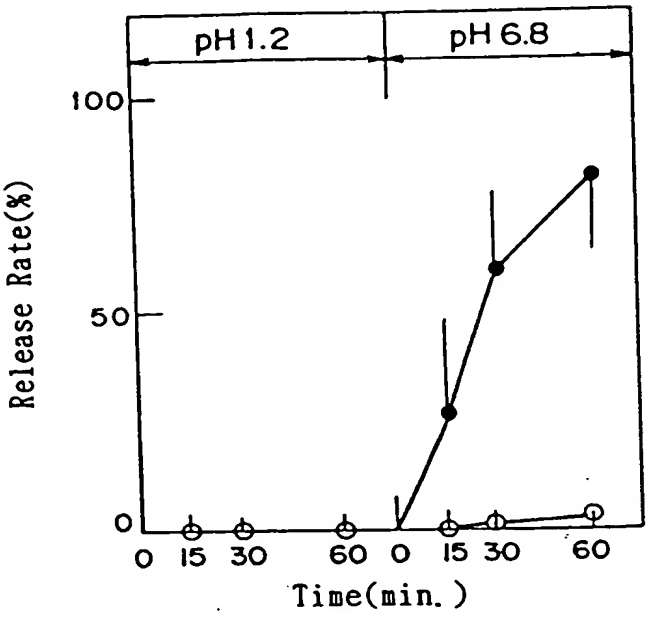


Fig. 5/6

Release behavior of indomethacin from pellets preparation of Example 8(A) or Example 11(B)

(A)



(B)

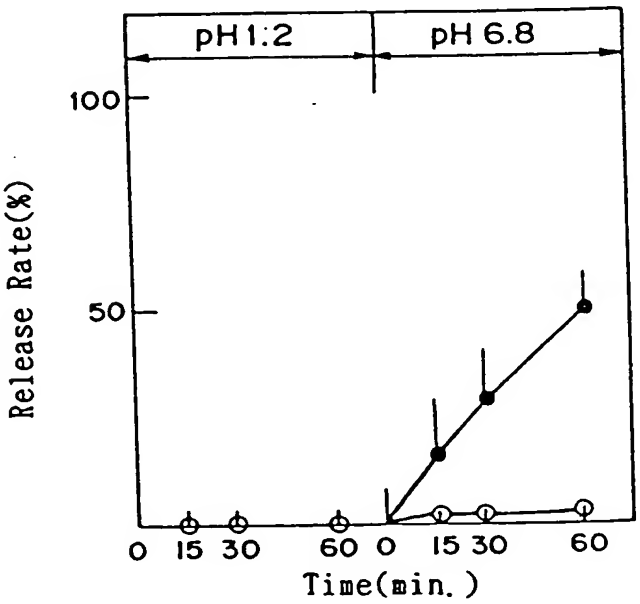
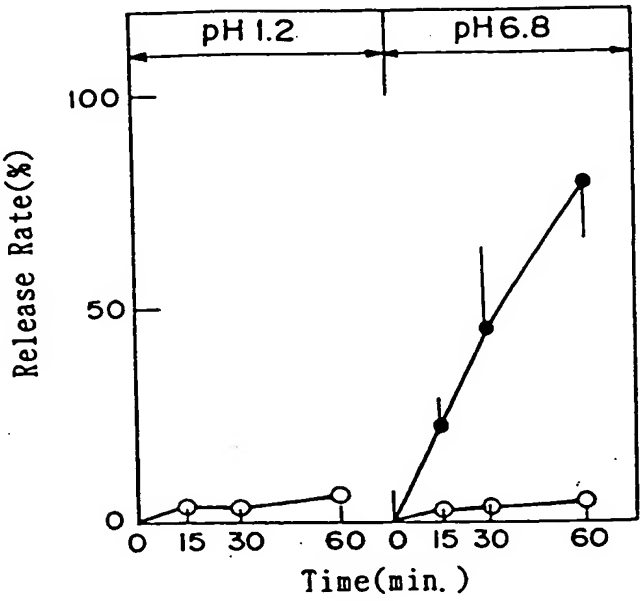


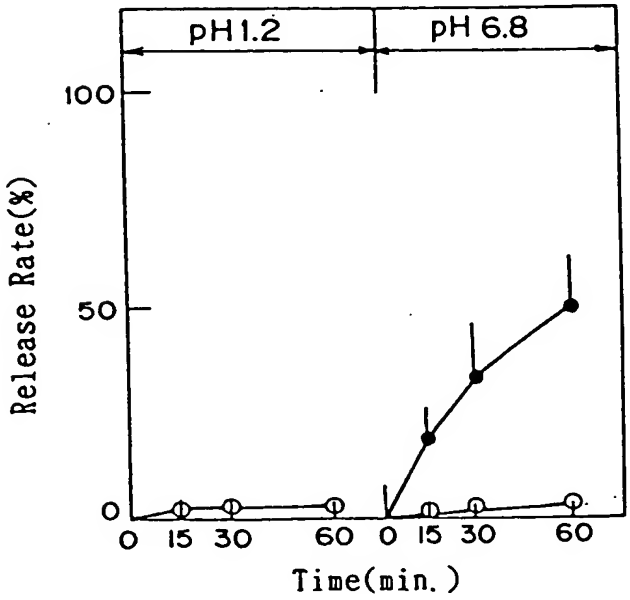
Fig. 6/6

Release behavior of U-78875 from pellets preparation of Example 9(A) or Example 12(B)

(A)



(B)



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/05245

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/48; A61K9/16; A61K31/495; A61K31/425

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,3 374 146 (BLICHARZ M.S. ET AL) 19 March 1968 see column 1, line 49 - column 2, line 39 see column 2, line 63 - line 72 see column 3; example 2 see claim 1	1,2
Y	---	3
X	EP,A,0 274 870 (T.I.L. MEDICAL LTD) 20 July 1988 see page 4, line 7 - line 29 see page 13 - page 14; examples 1,3	1,2

X	DE,A,2 439 538 (LUDWIG HEUMANN & CO GMBH) 4 March 1976 see page 1, paragraph 1 - page 2, paragraph 1 see page 5 - page 6; example 1	1

	-/--	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 OCTOBER 1992	29. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BOULOIS D.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0 320 136 (A/S FERROSAN) 14 June 1989 see page 7, line 22 - line 48 see page 11, line 24 - line 26	3

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9205245 SA 62010

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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EP-A-0274870	20-07-88	AU-B-	605812	24-01-91
		AU-A-	8263987	23-06-88
		JP-A-	63277617	15-11-88
		US-A-	4944949	31-07-90
DE-A-2439538	04-03-76	None		
EP-A-0320136	14-06-89	AU-A-	2660288	08-06-89
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		US-A-	4968682	06-11-90
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